Expanding BCS-Based Biowaivers

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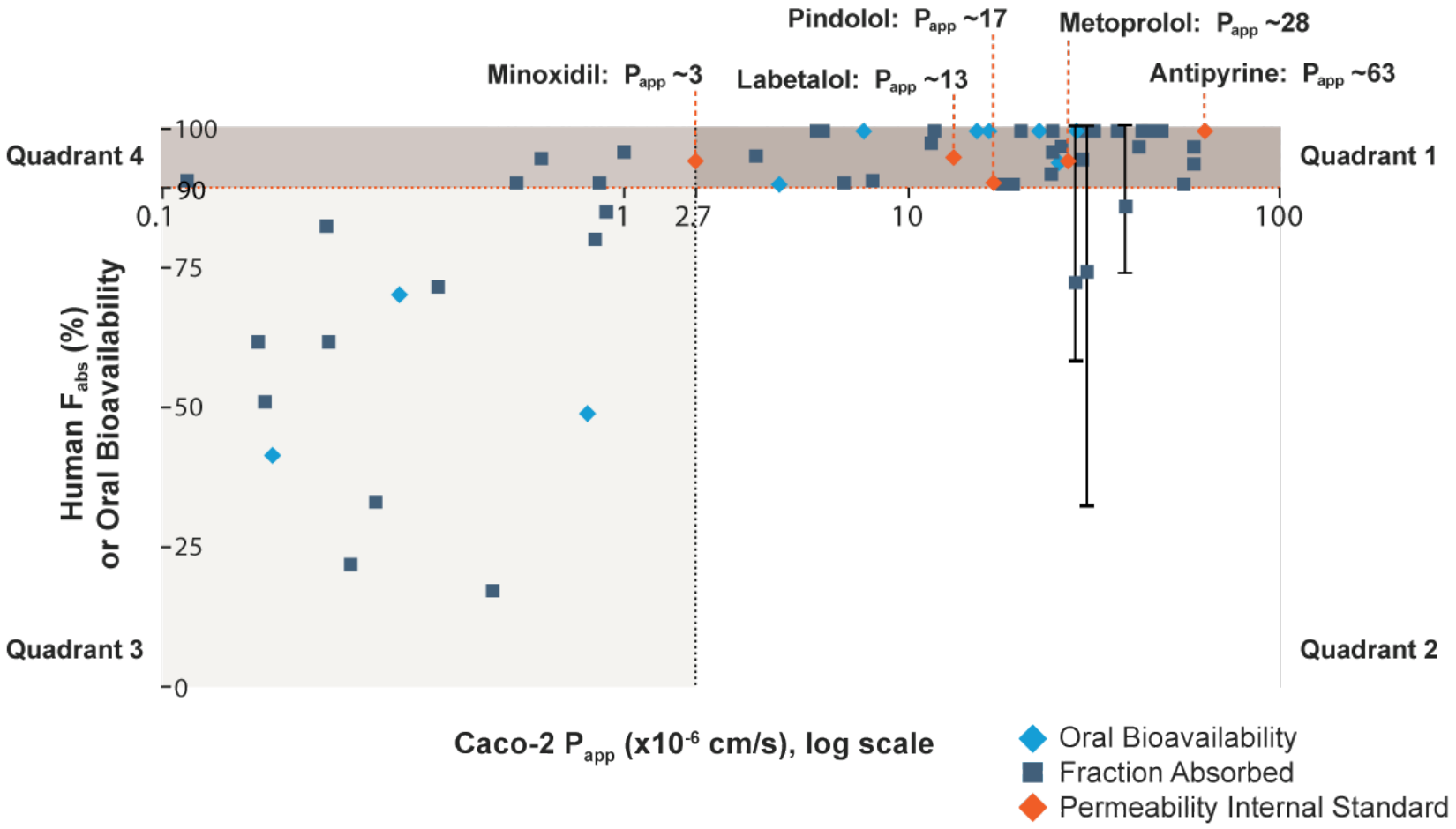
May 16, 2014

ABSORPTION® SYSTEMS

Utilization of BCS Biowaivers

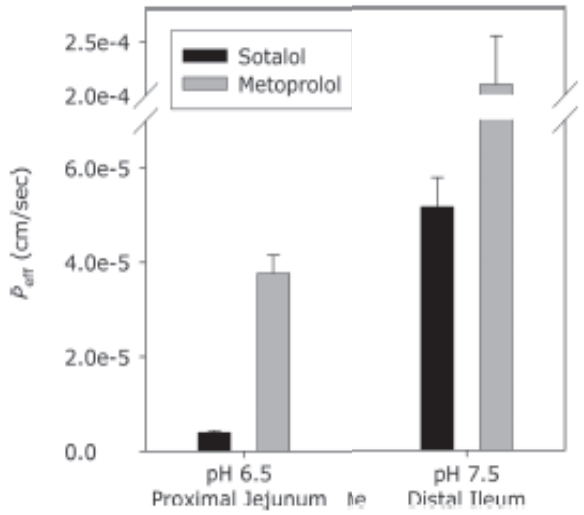
- Current initiatives
- Expansion within BCS I
- Next steps
    - Permeability
    - Solubility
    - Awareness

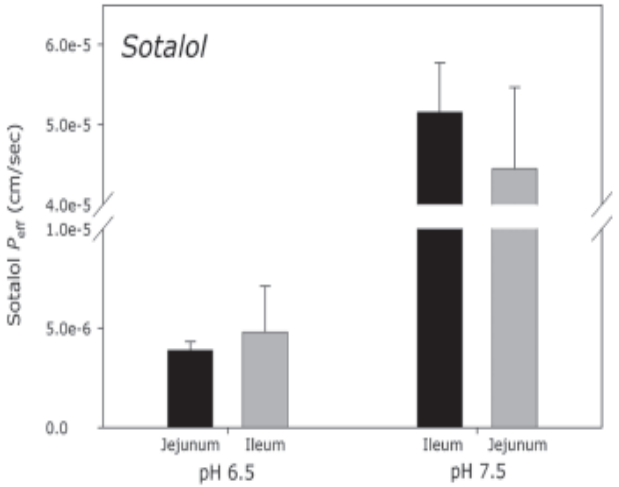
Permeability Progress: Internal Standard



Permeability Progress: pH

- Local vs. Average Permeability
- More accurate classification conditions



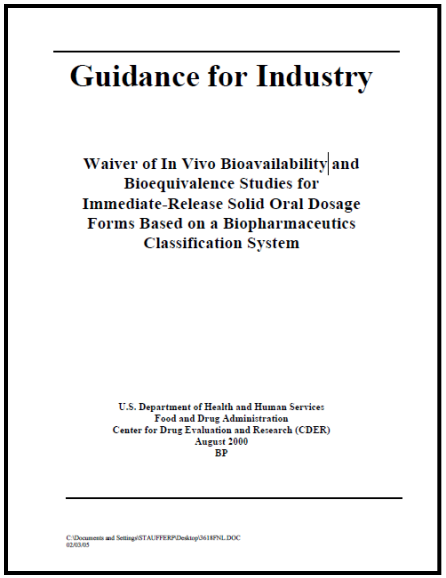


Dahan et al., Molecular Pharmaceutics, May 2010

Possible extension of high permeability:

"..if a compound matches/exceeds this threshold **anywhere in the intestine**, and not necessarily in the jejunum, it is a high permeability compound."

Permeability Limitation: Passive



Guidance for Industry

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2000
BP

C:\Documents and Settings\STAUFFER\Desktop\3618FNL.DOC
02/03/05

For application of the BCS, an apparent passive transport mechanism can be assumed when one of the following conditions is satisfied:

- A linear (pharmacokinetic) relationship between the dose (e.g., relevant clinical dose range) and measures of BA (area under the concentration-time curve) of a drug is demonstrated in humans
- Lack of dependence of the measured in vivo or in situ permeability is demonstrated in an animal model on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 ml) in the perfusion fluid
- Lack of dependence of the measured in vitro permeability on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 ml) is demonstrated in donor fluid and transport direction (e.g., no statistically significant difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction for the drug concentrations selected) using a suitable in vitro cell culture method that has been shown to express known efflux transporters (e.g., P-gp)

Case Study #1

	Low	Mid	High
Efflux Ratio < 3	✓	✓	✓
P_{app} > Minoxidil	✓	✓	✓

- Passive transport
- No need for additional clinical data supporting dose linearity
- Non-clinical test system sufficiency confirmed

Case Study #2

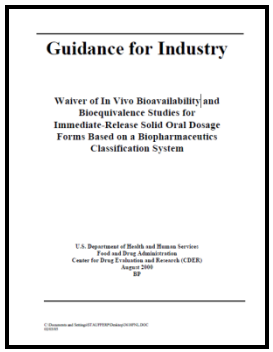
	Low	Mid	High
Efflux Ratio < 3	X	✓	✓
P_{app} > Minoxidil	✓	✓	✓

- Alternate pH conditions
- Confirm symmetry with dose linearity data

  Apply efflux inhibitor

Changing Perspectives on Active Transport

2000



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- Limited to passively permeable compounds

cyclosporin A, vinblastine, rhodamine 123). An acceptance criterion for intestinal efflux that should be present in a test system cannot be set at this time. Instead, this guidance recommends limiting the use of nonhuman permeability test methods for drug substances that are transported by passive mechanisms.

FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.

2005

Commentary

Predicting Drug Disposition via Application of BCS: Transport/Absorption/Elimination Interplay and Development of a Biopharmaceutics Drug Disposition Classification System

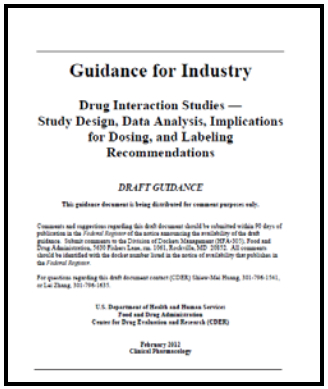
- No significant transporter effects for highly permeable compounds

and liver following oral dosing of drugs (1,13). For class 1, highly soluble—high permeability rate—extensively metabolized drugs, transporter effects in the intestine and the liver have no clinical impact. Even compounds like verapamil,

Benet et al. 2005. Predicting Drug Disposition via Application of BCS . Transport/Absorption/Elimination Interplay and Development of a Biopharmaceutics Drug Disposition Classification System.

Changing Perspectives on Active Transport

2006



Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

DRAFT GUIDANCE

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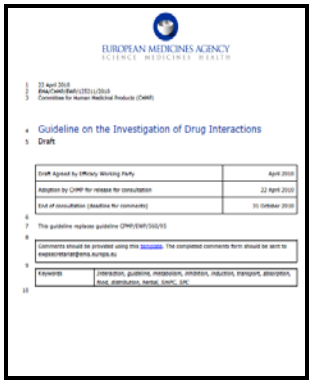
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2012
Clinical Pharmacology

2010



EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

Guideline on the Investigation of Drug Interactions

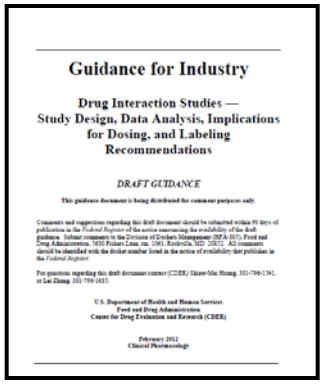
Draft

Draft Agreed by Efficacy Working Party	April 2010
Adoption by CHMP for release for consultation	22 April 2010
End of consultation (deadline for comments)	31 October 2010

This guideline replaces guideline CPMP/EWP/560/95

Keywords	Interaction, guideline, metabolism, inhibition, induction, transport, absorption, food, distribution, renal, CHMC, DIC

2012



Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

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February 2012
Clinical Pharmacology

- *In vitro* systems well accepted for studying transporter interactions
- Conservative system: Negative results preclude clinical testing.
- Clinical exceptions for Class I compounds:
  - AUCi/AUC cannot be ≥ 1.25

For drugs that are highly permeable and highly soluble, the intestinal absorption is not a rate-limiting step, and, therefore, it may be appropriate to exempt such drugs from the in vivo evaluation with a P-gp or BCRP inhibitor. (For further discussion regarding the

FDA Guidance for Industry (2012): Drug Interaction Studies

Exaggerated *In Vitro* Efflux

P_{app} ($x10^{-6}$ cm/s)	Duodenum	Jejunum	Ileum	Proximal Colon	Distal Colon	Caco-2
A→B	0.45	1.25	1.22	0.93	0.88	0.43
B→A	3.82	12.67	17.93	13.51	13.00	28.6
Efflux Ratio	8.55	10.14	14.70	14.54	14.75	66.5

•Absorption Systems Report No. 10ASLP_Pgp Substrate. P-gp substrate validation report, Oct 2010.
•Wang, X., Guerra, F., Joseph, J., Huang, Y., Winans, J., Bhoopathy, S., Hidalgo, I.J., and Weiskircher, E., Ex Vivo Evaluation of Regional Differences in the Expression and Function of Active Drug Transporters and Metabolic Enzymes in Rat and Human Intestine. Poster presented at 2010 AAPS Annual Meeting.

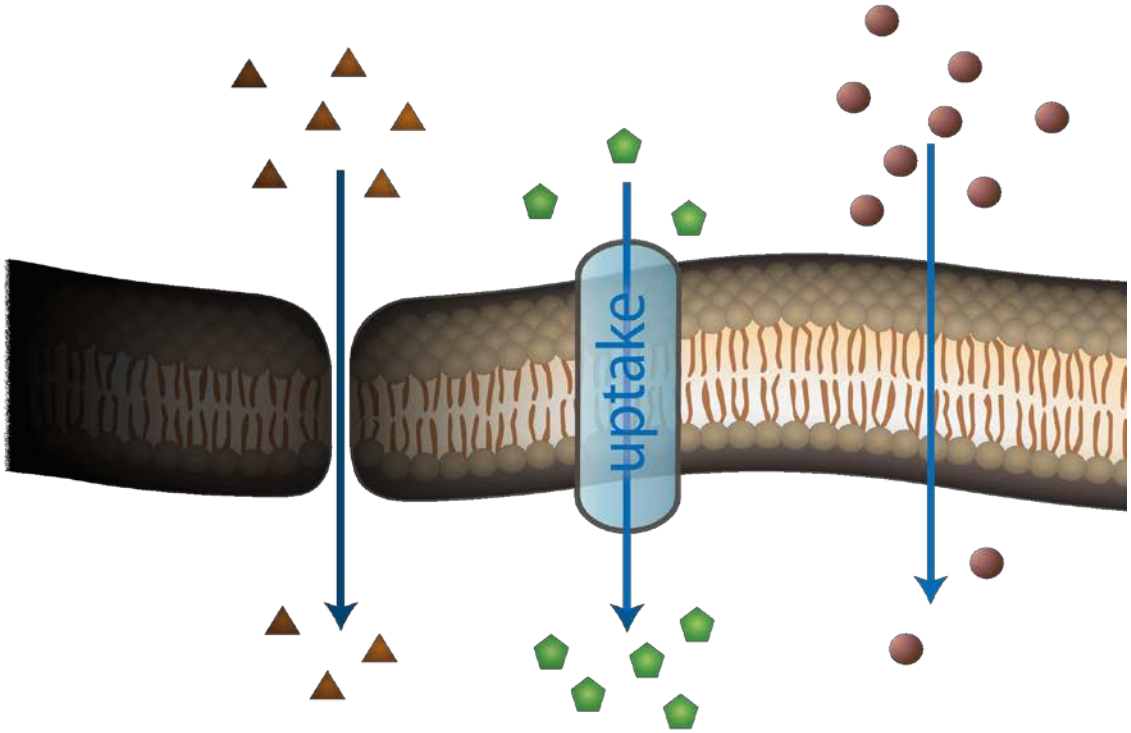
Permeability Constituents

Total Absorption Rate = Carrier-Mediated + Membrane + Paracellular* + Transcytosis*

$$J_e = J_c + J_m + J_p + J_t$$

$$J_c = \frac{J_{max} * C}{K_m + C}$$

$$J_m = P_m * C$$



Clinical Waiver of Transporter Studies

"…If the permeability in the absence of transporters is **high** (≥ the permeability constant of the highly permeable drug metoprolol) **the effect of active drug transport will be negligible as compared to the passive concentration-gradient driven absorption of the drug"**

$$J_e = J_c + J_m$$

↓ when $J_m >> J_c$

$$J_e = J_m$$

J_e : effective flux

J_c : carrier-mediate flux

J_m : passive flux

Guideline on the Investigation of Drug Interactions EMA/CHMP/EWP/125211/2010

Case Study #2 - Revisited

	Low	Mid	High
Efflux Ratio < 3	X	✓	✓
P_{app} > Minoxidil	✓	✓	✓

- Alternate pH conditions
- Confirm symmetry with dose linearity data

  Apply efflux inhibitor

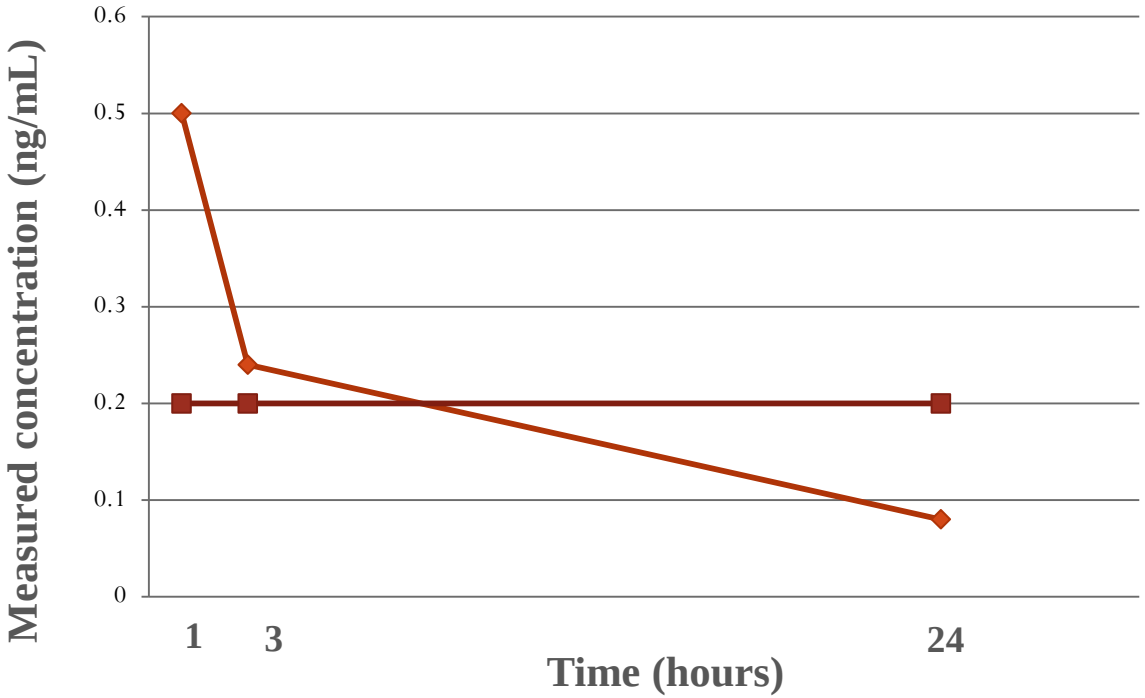
Does this efflux matter?

Case Study #3

	Low	Mid	High
Efflux Ratio < 3	X	X	X
P_{app} > Minoxidil	X	✓	✓

- Asymmetry superseded by intrinsic membrane permeability
- Does 1% of the highest dose strength matter for permeability classification?

Solubility Limitations: Duration



- pH Range: Physiologically Relevant
- Temperature: Physiologically Relevant
- **Duration: Equilibrium?**

Solubility Limitations: pH

pH	Concentration (mg/mL)
1.0	5.36
3.0	5.47
5.0	4.87
6.8	4.54
7.2	4.46
7.5	1.19

- Target solubility: 1.6mg/mL

Clarifying Expectations

Guidance for Industry
ANDA Submissions —
Refuse-to-Receive Standards

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 30 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Johnny Young, 240-276-8677.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2013
Generic Drugs

2. Waiver of in vivo BA or BE studies for BCS Class I Drugs

Refer to FDA's guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* for details regarding waivers of any required in vivo bioavailability (BA) or BE studies based on a Biopharmaceutics Classification System (BCS) Class 1 drug substance.

If any of the data needed to support a waiver request are missing from the ANDA at the time of submission, FDA will refuse to receive the ANDA based on insufficient evidence to support a BCS Class 1 BA/BE waiver request. However, FDA may deny a BA/BE waiver request based on a BCS Class 1 drug substance even with inclusion of these data if there are other factors present that would negatively affect the waiver request. Such a decision will result in FDA refusing to receive the ANDA.

Spreading Awareness

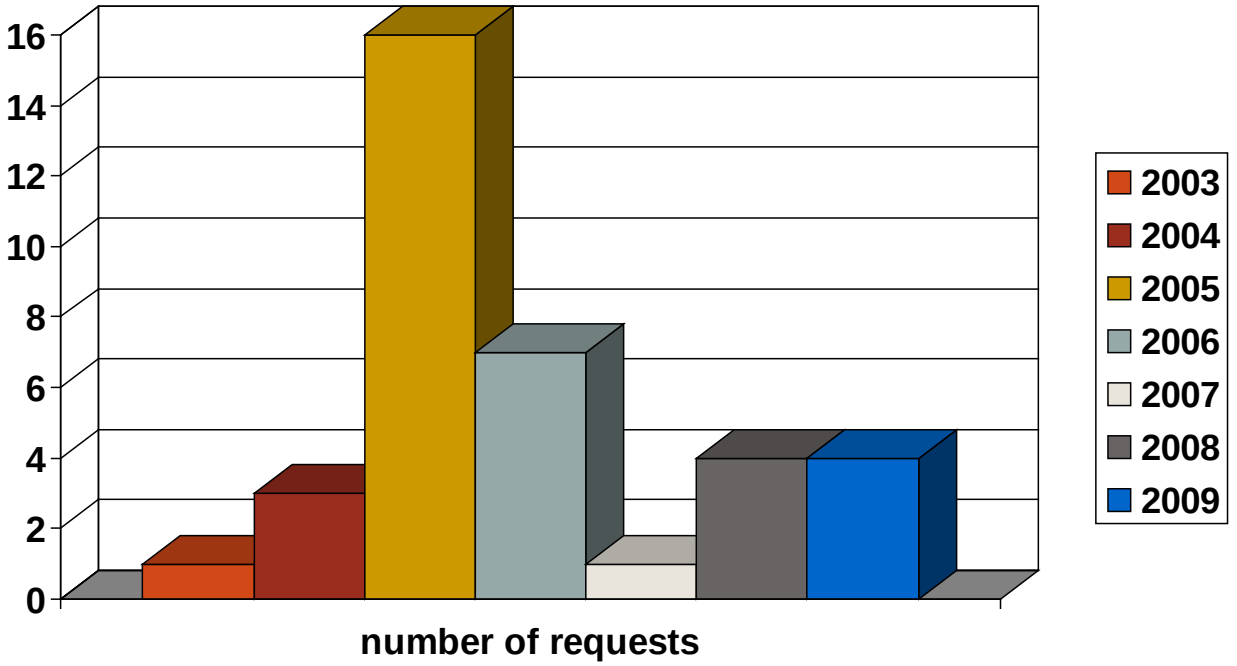
Common Perceptions about BCS

- Generic:
  - Perceived as competitive disadvantage
  - Fear of delayed approval/RTR
  - Confusion about applicability
- Brand:
  - Useful for QbD, formulation development, re-positioning
- Academic
  - Concerns about variability and over-simplification

Milne, et. al. FDA' Biopharmaceutics Classification System: Evolution or Devolution (2011)

Stimulating BCS-Based Biowaivers

BCS Biowaiver Submissions Reviewed by FDA OGD



Barbara Davit "An Update on the BCS Review Process at the US-FDA Session" , Biowaiver Based on BCS ANVISA, Brasilia, Brazil, September 15, 2009